an effective amount of an antibody as claimed in claim 13 and a pharmaceutically acceptable carrier.

18. A pharmaceutical composition which may be used in treatment comprising as an active ingredient the polypeptide as claimed in claim 2 and a pharmaceutically acceptable carrier.

19. A pharmaceutical composition which may be used in treatment comprising as an active ingredient the nucelic acid as claimed in claim 11 and a pharmaceutically acceptable carrier.

34. A method of culturing cells which may be used in treatment, comprising adding to a cell culture comprising said cells a cell growth-stimulating amount of v-IL-6.

35. The method of claim 34, wherein said cells which may be used in treatment are selected from the group consisting of ß-lymphocytes, hybridomas, hemopoetic and endothelial cells.

REMARKS

Applicants respond to a first Office Action on the merits mailed on October 3, 2000 following a restriction requirement mailed on April 14, 2000. Claims 1-20 and 28-35 have been pending and stand rejected on various grounds.

In this response, applicants cancel claim 7, amend claims 1-4, 8-11, 16-19 and 34-35. Reconsideration and allowance of claims 1-6, 8-20 and 28-35. are earnestly requested.

Objections to the Specification

On page 2 of the Office Action the Examiner has requested that the specification be arranged with new section headings. In response, applicants have inserted new headings and provide a revised specification pages with those headings as Appendix A.

On page 3 of the Office Action the Examiner further objects to the disclosure. In response, Applicants have amended the specification as requested by the Examiner.

The term "b1" on page 4 is objected to. In response, applicants amend the typographical error "b1" to become "b."

The phrase "shall be comprised" on page 4, last line of part I, is objected to. In response, applicants replace this improper grammar with the more correct grammar "is provided."

The phrase "v-IL-6 or the polypeptide" on page 5, part p, is objected to. In response, applicants amend the improper grammar "the polypeptide, which can be obtained" to "the polypeptide that can be obtained" to more clearly indicate that both v-IL-6 and certain polypeptides are both contemplated as active ingredients.

The term "auxilliary" in part r has been changed to "auxiliary."

The term "hemopoetic" on page 6, part v has been changed to "hemopoietic."

The spelling and capitalization of "californiа" has been corrected.

The reference to the Dayhoff Model on page 7, under Figure 1 as "by M. Dayhoff" has been changed to "in the Dayhoff Model." Applicants point out that the "Dayhoff" model for determining conservative amino acids and the symbolization used by Dayhoff is well known. A representative publication that summarizes the Dayhoff Model is attached as Appendix B. Please see p. 12 of that 22 page document.

Objections to the Claims

On page 3 the Examiner has required correction of the term "competively" used in Claim 8. In response, applicants have amended claim 8 to recite "competitively."

Rejection under 35 U.S.C. 101

At the bottom of page 3 through the top of page 4 the Examiner has rejected claims 1-3 as reading "on proteins/polypeptides which are found in nature" and suggest the addition of the qualifier "isolated." In response, applicants have amended claims 1-3 to recite "isolated."

Reconsideration and allowance are requested.

Rejection under 35 U.S.C. 112, Written Description

On page 4 of the Office Action the Examiner has rejected claims 4-7, 8, 12, 18, 19, 34 and 35 as failing to meet the written description requirement. Specific reasoning is provided in pages 4 through 9.

a. On pages 4 and 5 of the Office Action, the Examiner rejects claims 18 and 19 for reciting the terms "pharmaceutical composition" and "pharmaceutically acceptable carrier." The Examiner contends that the specification does not provide written description for these terms. In response, applicants have amended claims 18, 19, 34 and 35 to recite "A composition which may be used in treatment comprising…." The term "which may be used in treatment" is found in the second to third lines of the specification as filed and does not constitute new matter. Reconsideration and allowance are earnestly solicited.

b. At pages 5 and 6 of the Office Action, the Examiner rejects claims 4-7 for lack of support in the specification. In particular, the Examiner alleges that the phrase "the capacity of binding to an IL-6 receptor" is scientifically unsound. For instance, the Examiner refers to several publications showing that viral IL-6 binds to gp130, not the IL-6 receptor. The thrust of the Examiner's argument appears to be that another protein, gp130 is known to bind IL-6, and that therefore, IL-6 does not bind the IL-6 receptor.

Applicants appreciate the Examiner's observation that gp130 binds to IL-6 and note that BOTH gp130 and the IL-6 receptor bind IL-6. Although gp130 also binds as well, IL-6 binds to IL-6 R

with a Kd = 5.5 nM, and this low affinity complex is still known to subsequently recruit a gp130 molecule to form a high-affinity complex with a Kd = 50 pM. (See Hibi, M. *et al.* (1990) *Cell* **63**:1149).

Also see Burger,R., F.Neipel, B.Fleckenstein, R.Savino, G.Ciliberto, J.R.Kalden, and M.Gramatzki. 1998. Human herpesvirus type 8 interleukin-6 homologue is functionally active on human myeloma cells. *Blood* 91:1858-1863 and Li,H., H.Wang, and J.Nicholas. 2001. Detection of Direct Binding of Human Herpesvirus 8-Encoded Interleukin- 6 (vIL-6) to both gp130 and IL-6 Receptor (IL-6R) and Identification of Amino Acid Residues of vIL-6 Important for IL-6R-Dependent and - Independent Signaling. *J.Virol.* 75 :3325-3334. The two latter publications show that vIL-6 not only binds to gp 130 but also to gp 80 (Burger *et al.*, fig. 3, page 1860: The proliferative activity of hIL-6 as well as vIL-6 on INA-6 cells was almost completely inhibited by a combination of neutralizing antibodies specific for the human IL-6R (gp80) and the gp130 molecule. Thus, it is obvious that gp 80 significantly adds to the effect observed. In particular, see the passage on page 1860 headed "Effect of IL-6R superantagonist Sant7 on hIL-6 and vIL-6".

It is well known that IL-6 binds to the IL-6 receptor separate from IL-6 binding to gp130. For example, soluble IL-6 receptor binds circulating IL-6 and extends its half-life, and, on the surface of cells expressing gp130, it forms a signal transducing complex [for example, see Kishimoto, T. *et al.* (1995) Blood **86**:1243].

The biology of IL-6 binding to its receptor and the interaction of gp130 are still well accepted in the year 2001. For example, a review of this field was found on March 29, 2001

at "www.rndsystems.com/asp/r_il6_mini.asp," which in turn was first published in a catalog for R&D workers in 1999. A copy of the March 29, 2001 published review is attached as Appendix C.

In view of the fact that IL-6 binds to its receptor with a known affinity and acceptance of the fact that IL-6 binds to its receptor as well as with gp130, it is respectfully requested that this rejection be withdrawn.

c. At pages 6 and 7 of the Office Action, the Examiner rejects claim 7, contending that the specification lacks objective evidence as to what kind of mutants or variants of v-IL-6 would be functionally equivalent to v-IL-6. Applicants have cancelled claim 7 in order to argue the contested claim language at another time, mooting the present rejection. Reconsideration and allowance are requested.

d. At page 7 of the Action, the Examiner rejects claim 8, alleging that the specification does not convince one of skill in the art that at the time the application was filed, applicants had possession of the claimed fragments. At pages 10-11 of the Action, the Examiner also rejects claim 8 as not being enabled for the recitation of "a suitable assay system."

In response, applicants point out that the knowledge of how to determine what fragments work, and, more importantly which fragments can bind to the receptor and competitively inhibit native binding of IL-6 in vivo previously was known. For example, see the discussion on page 2 of Appendix C. Suitable

assay systems, as exemplified in the references listed on Appendix C were known in the art on the filing date of the present application. Applicant has no obligation to repeat what is known and did not include all such details in a patent application for the sake of brevity. Reconsideration and allowance are requested.

e. At pages 7-9 of the Office Action, the Examiner rejects claim 12 as lacking written description for the term "hybridizing under stringent conditions." In addition, at pages 16-18 of the Action, the Examiner rejects claim 12 as being anticipated by Zhong *et al.* (*Proc. Natl. Acad. Sci.* U.S.A. 93:6641-6646, June 1996), Chang *et al.* (*Science*, 266:1865-1869, 1994) in light of Chang *et al.* (U.S. Patent No. 5,831,064, 1998), or Ganem *et al.* (U.S. Patent No. 5,861,240).

Applicants note that the concept of stringency, used to describe hybridization conditions inherently is present in the specification and believe that the concept is present in one or more of the cited publications. In this context, Applicants note that Figure 1 provides data relating to stringency. Figure 1 shows the consensus obtained between IL-6 human, IL-6 mouse and IL-6 hhv8, and further shows positions of greater and less great homology. Stringency of hybridization is one aspect of this comparison, with greater stringency being associated with greater homology shown in Figure 1 and lower stringency being associated with lesser homology.

Reconsideration and allowance are requested.

f. On pages 9 and 10 of the Office Action, the Examiner rejects claims 4-6 as not being enabled. Specifically, the Examiner contends that a skilled artisan would not know if the claimed fragment is capable of binding to an IL-6 receptor because "Molden et al., Wan et al., Mullberg et al., and Hoischen et al., teach that the v-IL-6 of human herpesvirus 8 does not bind to the IL-6 receptor.

In response, applicants point out that the binding of the entire v-IL-6 from the virus differs more from the structure of the human IL-6 than does the precise binding region described on page 2 middle of the specification, particularly amino acids 105 to 123. Accordingly, comparisons of the entire proteins with each other, which include more differences, are not relevant to the comparisons of the binding portions. Applicants prefer the use of fragments that comprise the binding portion partly for this reason.

Reconsideration and allowance are earnestly requested.

g. On page 11 the Examiner has rejected claim 12. Applicants point out that the term "stringent" is well known and that such conditions were well known and available to a skilled artisan on the filing date. For example, see Casey, J. and N. Davidson. 1977. Rates of formation and thermal stabilities of RNA:DNA and DNA: DNA duplexes at high concentrations of formamide. *Nucleic Acids Res.* 4:1539-1552. Another reference that demonstrates the state of the art before filing is the well known textbook of Maniatis *et al.*: "Molecular Cloning", Second Edition, Cold Spring Harbor Laboratory Press (1989).

Applicants note that the sequence of the nucleic acid that is hybridizable is known and that information known to the reader easily supplies suitable conditions for hybridization. Reconsideration and allowance are requested.

h. On pages 11 and 12 of the Office Action, the Examiner has rejected claims 18 and 19 on enablement grounds. Applicants have removed the term "pharmaceutical compositions" from these claims. Reconsideration and allowance are requested.

i. At pages 12 and 13 of the Office Action, the Examiner rejects claims 20, 34 and 35 as not being enabled because "the specification does not disclose the functional activity of v-IL-6 or what a cell growth stimulating amount of v-IL-6 encompasses."

In response, applicants point out that they provide a guide to using v-IL-6 and fragments of v-IL-6. The specification teaches (for example, see the middle of page 2) that the desired property of v-IL-6 arises from the homology to human IL-6, including an "area involved in binding of human IL-6 to its receptor (which) has been mapped to the middle of the protein" and that this inherently explains a one to one molar correspondence between v-IL-6 and IL-6, which have high homology in this region and are overall homologous. Furthermore, as is evident from the references supplied by the Examiner and the references on Appendix C, a number of workers in this field are familiar with "suitable cell culture media and suitable cell culture conditions" from the copious documentation by skilled artisans before the priority date of the application. A skilled

artisan would understand the teaching of a one-to-one molar correspondence between peptide and proteins having the region between amino acids 105 to 123 and the extant conditions for using the SAME molar amounts of protein (as human IL-6) having the same region 105-123.

Reconsideration and allowance are requested.

j. At page 13 of the Office Action, the Examiner rejects claim 28 as not being enabled. The Examiner contends that the specification does not disclose how to make a polynucleotide that comprises the amino acid sequence of Figure 2. However knowledge of how to make a nucleic acid that codes for a particular amino acid sequence is well established. If necessary, applicants volunteer to provide research papers and review articles on this topic.

Reconsideration and allowance are requested.

k. At pages 14-16 of the Office Action, the Examiner claims 1 and 2 and those dependent thereon as being indefinite for reciting "which can be obtained." In response, applicants have removed this phrase. Reconsideration and allowance are requested.

l. On page 14, the Examiner argues that claims 2, 3, 10 and 28 are indefinite because "there is no amino acid sequences set forth in Figure 2." In response applicants explain that the sequences of Figure 2 are on pages 3/4 and 4/4. Reconsideration and allowance are requested.

m. On page 14, the Examiner argues that claim 4 is indefinite for reciting "having the capability of binding." In response, the phrase has been replaced by "that binds." Reconsideration and allowance are requested.

n. On page 14, the Examiner argues that claims 4 and 5 are "indefinite by the use of upper case and lower case letters….." Applicants point out that Figure 1 of the specification illustrates use of upper and lower case letters to denote which amino acids differ from IL-6. Figure 1 shows that the lower case letter labelled amino acids are known to readily differ among homologous proteins because an inspection of this figure indicates a side by side comparison, as is customary in this field of art. Reconsideration and allowance are requested.

o. On page 14, the Examiner argues that claim 8 is indefinite for lack of an antecedent basis. In response, applicants have amended claim 8 to make the claim independent. Reconsideration and allowance are requested.

p. On page 15, the Examiner argues that claim 16 is indefinite because of recitation of a nucleic acid molecule of claim 11. Claim 11 describes Figure 2, which provides a nucleic acid that can hybridize to v-IL-6 DNA or RNA. Reconsideration and allowance are requested.

Rejection under 35 U.S.C. 102

a. At pages 16-18 of the Office Action, the Examiner rejects claims 9-12 and 16 as being anticipated by either Zhong *et al.* (Proc. Natl. Acad. Sci. U.S.A. 93:6641-6646, June 1996), Chang *et al.* (Science, 266:1865-1869, 1994) in light of Chang *et al.* (U.S. Patent No. 5,831,064, 1998), or Ganem *et al.* (U.S. Patent No. 5,861,240). However, neither of the above cited references specifically teaches an isolated nucleic acid consisting essentially of the sequence of v-IL-6, as described by the present invention.

Applicants note that no reference specifically teaches an isolated nucleic acid molecule consisting of the sequence of v-IL-6. To emphasize this difference, applicants have amended claims 9-11 and 16 to recite "A nucleic acid consisting essentially of the sequence of SEQ ID NO: 1." Reconsideration and allowance are requested.

b. At page 17 of the Office Action, the Examiner rejects claim 8 as being anticipated by Clark *et al.* (WO 88/00206, 1988). It appears that this rejection may be directed to claim 7, instead of claim 8. Claim 7 has been cancelled. Reconsideration and allowance are requested.

Objections to the Specification

On page 18 of the Office Action, the Examiner has objected to the sequence listing. In response, applicants have amended the specification as suggested by the Examiner. Reconsideration and allowance are requested.

Conclusion

Applicants submit that the present claims are in condition for allowance and respectfully request consideration to that effect. Should the Examiner have any questions regarding the present application or believe that further discussion will advance prosecution, the Examiner is invited to contact the undersigned at the number listed below.

Respectfully submitted,

April 3, 2001
Date

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